

Acute Diffuse Interstitial Nephritis Related to Chemotherapy of Tuberculosis

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Acute renal insufficiency developed in three patients receiving chemotherapy for tuberculosis. It is proposed that acute diffuse interstitial nephritis related to the drugs was responsible for the renal injury. Recovery of renal function was slow and incomplete. Physicians administering chemotherapy to patients with tuberculosis must be aware of the potential nephrotoxicity of the common treatment regimens.

Acute diffuse interstitial nephritis (ADIN) is a distinct clinicopathological entity comprising fever, decreasing renal function, hematuria, proteinuria, peripheral blood eosinophilia, and on histological examination mononuclear and eosinophilic infiltration of the renal interstitium without vasculitis or glomerulonephritis. ADIN usually occurs as a complication of an acute bacterial infection or hypersensitivity reaction to a drug (1, 2, 14). Bacterial infections that have been implicated in the development of ADIN include streptococcal sepsis, syphilis, leptospirosis, diphtheria, and brucellosis (2, 14). A number of drugs have been reported to cause this form of renal injury, most commonly penicillins, sulfonamide antibiotics, and sulfonamide diuretics (1, 10, 14).

ADIN has been reported as a toxic complication of rifampin therapy (4, 8, 12) but has not been commonly attributed to isoniazid, ethambutol, or streptomycin (1, 2, 5, 6, 10, 14). In two of the three cases reported herein, the clinical and, in one, the histopathological picture of ADIN occurred during the course of antituberculous therapy not including rifampin. The third patient was receiving isoniazid and rifampin when ADIN developed. These cases are reported to suggest that this form of renal injury may complicate antituberculous chemotherapy and to alert physicians to the necessity of monitoring renal function in patients being treated for tuberculosis.

CASE REPORTS

First case. A 52-year-old man was admitted to the Nashville Veterans Administration Hospital because of weakness, chills, productive cough, a chest X ray suggestive of cavitary tuberculosis, and a sputum smear positive for

acid-fast bacilli. Multiple initial sputum and urine cultures were positive for *Mycobacterium tuberculosis*. A urine analysis was normal, except for three to four leukocytes per high-power field. The serum creatinine was 1.4 mg/100 ml, and an intravenous pyelogram (IVP) was normal soon after admission.

The patient was treated with isoniazid (Kassar Laboratories), ethambutol (Myambutol; Lederle), and streptomycin (Tubex; Wyeth) beginning 8 May 1973. He regained his sense of well-being within 2 weeks of admission. Streptomycin was discontinued after 4 weeks because of vestibular toxicity. Urine cultures obtained on and after day 3 of treatment were negative for *M. tuberculosis*. Sputum cultures remained positive until week 16. The drug therapy is summarized in Table 1.

Renal insufficiency (serum creatinine of 4.8 mg/100 ml) was first noted during week 9 of hospitalization. Examination of the urine revealed 10 to 25 erythrocytes per high-power field, many coarse granular casts, and occasional tubular epithelial cells. Drug therapy at this time consisted of isoniazid, ethambutol, pyridoxine (50 mg daily), and one multiple vitamin capsule daily. No other drugs were being given. Despite the absence of symptoms and physical findings, renal function continued to deteriorate. The creatinine clearance fell from 65 ml/min on day 14 of hospitalization to 11 ml/min on day 97. Hypercalcemia (10.6 to 11.7 mg/100 ml) and peripheral blood eosinophilia were also noted (Fig. 1). The fluctuating eosinophil count may have been related to its computation from the total leukocyte count and the percentage of peripheral eosinophils. Proteinuria of 1 g/24 h was measured on one occasion. An IVP demonstrated no abnormalities except delayed

excretion of contrast material. There was no evidence of obstruction and the kidneys were normal in size and contour.

Renal biopsy was performed during week 11. Examination by light microscopy revealed a homogenous pattern of interstitial infiltration by lymphoid cells and eosinophils, increase in

intertubular connective tissue, and mild tubular atrophy (Fig. 2). The process was diffuse although more marked in some areas than in others. No areas of calcification were seen. All glomeruli were well preserved and free from lesions. Examination by electron microscopy revealed a predominantly lymphocytic interstitial infiltrate (Fig. 3). Dense deposits were observed within the tubular basement membrane, finely granular in character and consistent with morphological descriptions of immune complex deposits, including those seen in renal tubular disease in humans (3, 7). In some instances, interstitial foci of lymphocytes were found adjacent to tubular basement membrane deposits (Fig. 4). No glomerular abnormalities were seen. Immunofluorescent microscopy demonstrated small granular deposits of complement (C₃) along the tubular basement membrane. There was no glomerular staining and no evidence of deposition of antitubular basement membrane antibody.

The renal function of the patient slowly returned toward normal, but eosinophilia persisted (Fig. 1). Ethambutol and then isoniazid were discontinued. At the time of discharge, the antituberculous regimen consisted of rifampin and pyrazinamide, the patient felt well, and all cultures were negative for *M. tuberculosis*. However, significant renal insufficiency was still present (serum creatinine of 2.4 mg/100 ml

TABLE 1. Antituberculous drug therapy

Drug	Hospital days received	Dosage (g/day)
Case 1		
Ethambutol	1-64	1.6
	65-134	1.2
Isoniazid	1-191	0.3
Streptomycin	1-26	1.0
Rifampin	65-260	0.6
<i>para</i> -Aminosalicylic acid	142-157	6.0-15.0
Pyrazinamide	192-260	1.25-1.5
Case 2		
Ethambutol	1-73	1.2
Isoniazid	1-125	0.3
Streptomycin	1-15	1.0
Rifampin	73-125	0.6
Case 3		
Isoniazid	2-56	0.3
Streptomycin	70-200	0.3
Rifampin	2-58	0.6
Pyrazinamide	129-200	2.0

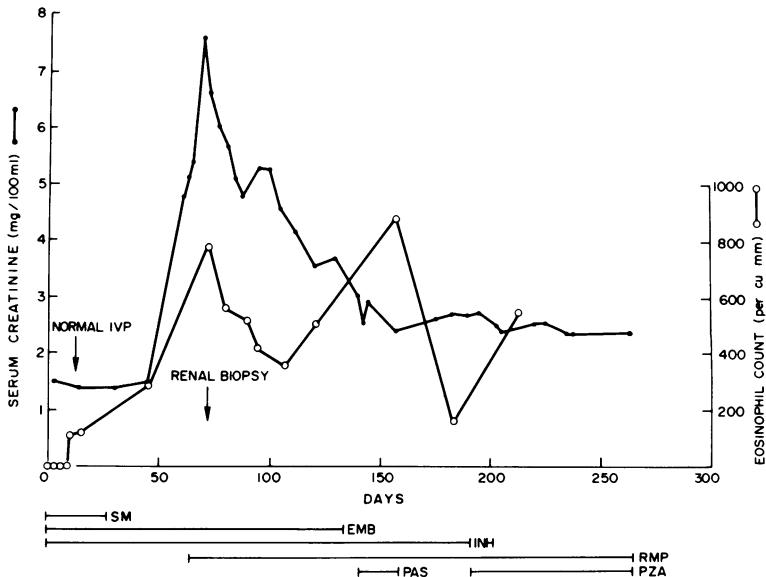


FIG. 1. Clinical course of the first patient in relation to drugs received. Note the sudden appearance of eosinophilia and renal insufficiency while the patient was being given only isoniazid and ethambutol. SM, Streptomycin; EMB, ethambutol; INH, isoniazid; RMP, rifampin; PAS, *para*-aminosalicylic acid; PZA, pyrazinamide.

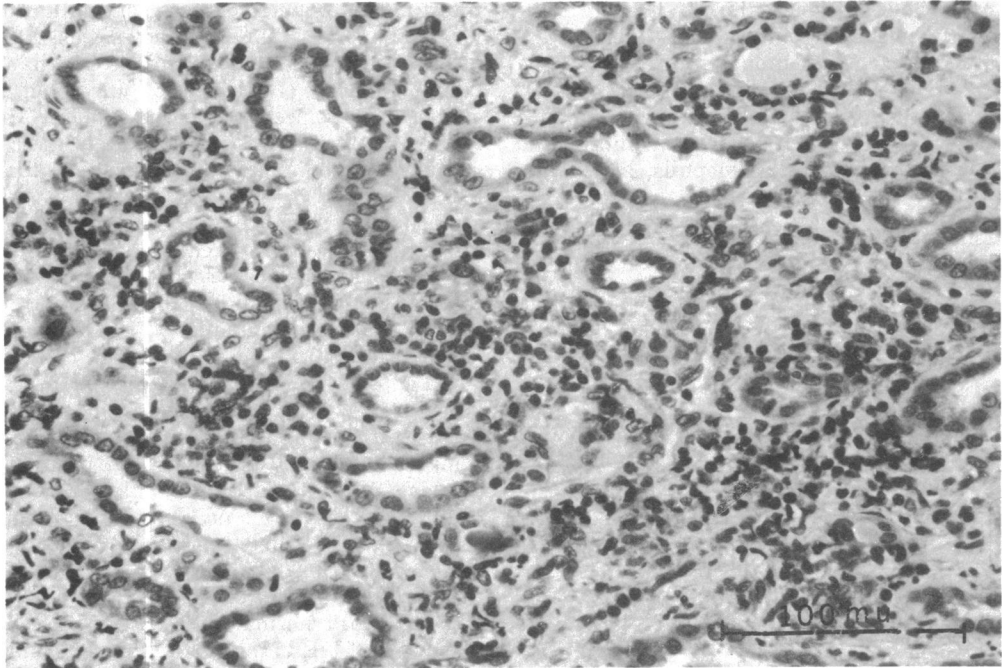


FIG. 2. Interstitium of the kidney shows moderate fibrosis, a diffuse lymphoid infiltrate, and moderate tubular atrophy. Hematoxylin and eosin stain. $\times 320$.

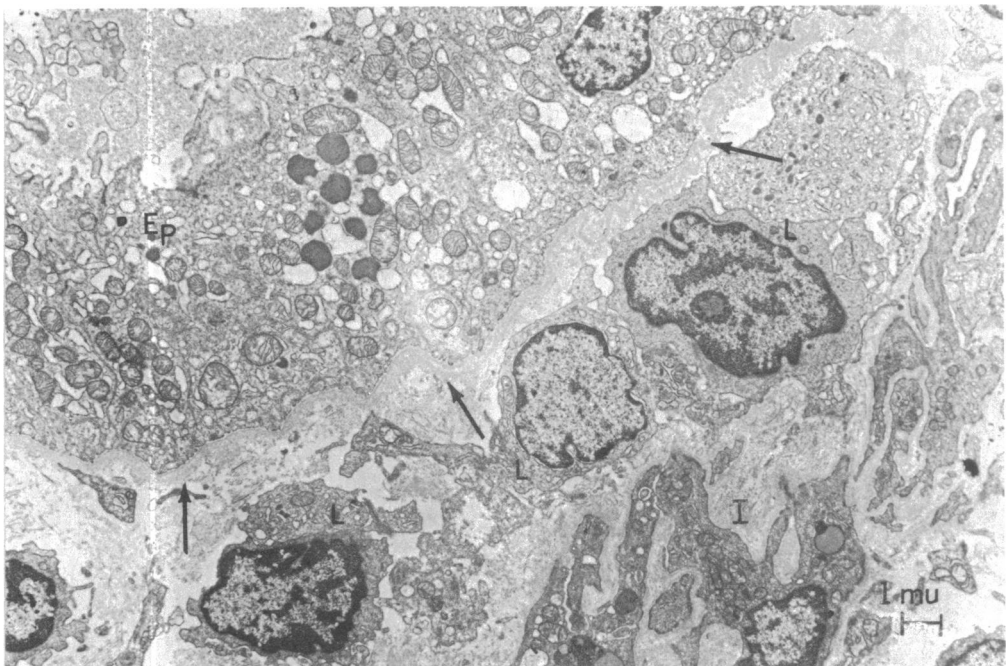


FIG. 3. Three lymphocytes are present in the interstitium (I), adjacent to the basement membrane (arrows). Uranyl acetate and lead citrate. $\times 4,600$. Ep, Tubular epithelium; L, lymphocytes.

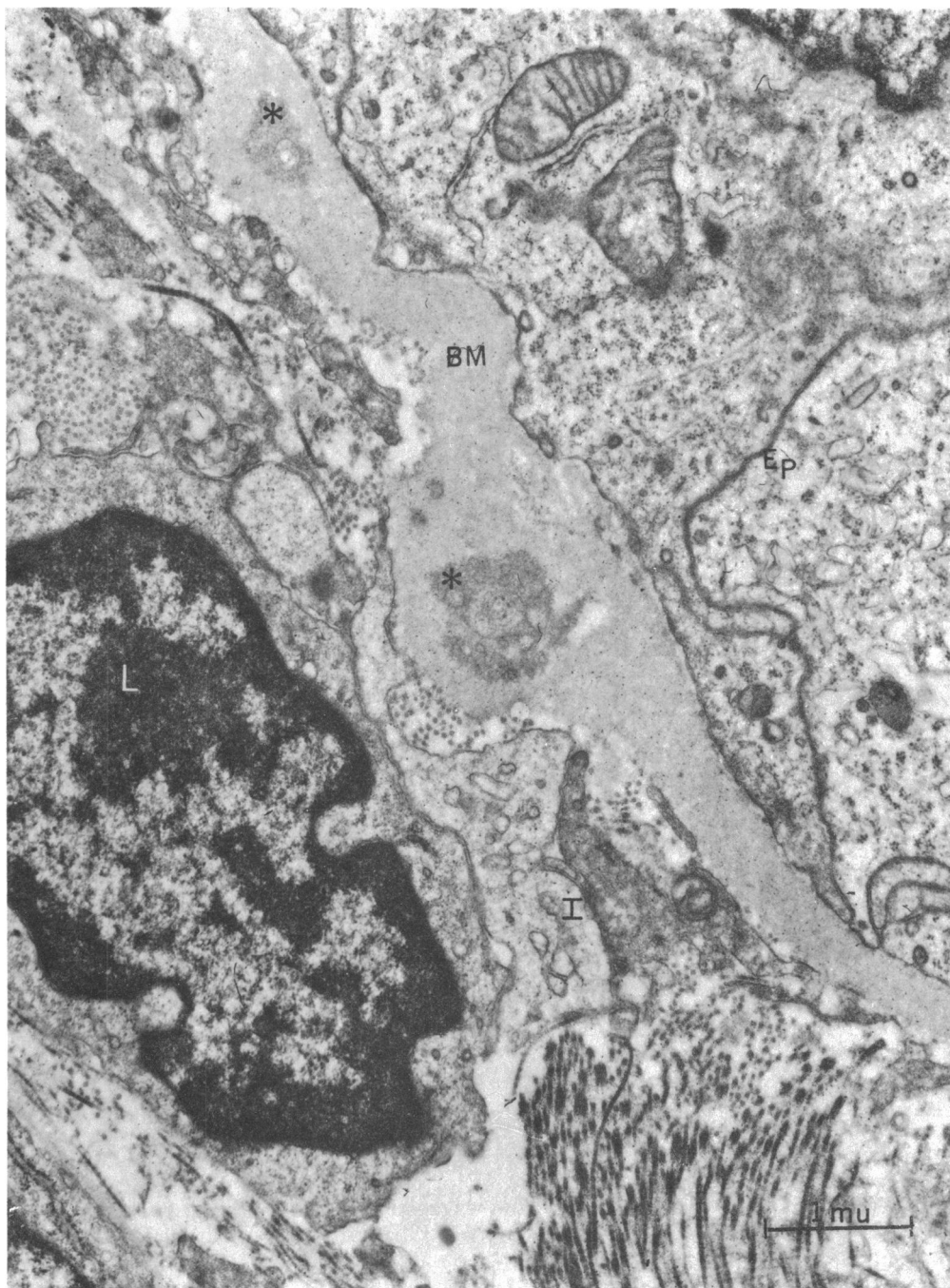


FIG. 4. Two deposit-like densities (asterisks) are present within the basement membrane (BM) of the tubular epithelium (Ep). A lymphocyte (L) is present in the adjacent interstitium (I). Uranyl acetate and lead citrate. $\times 19,000$.

and creatinine clearance of 32 ml/min). After 26 months his serum creatinine was 1.9 mg/100 ml.

Comment. This patient developed an acute

loss of renal function at a time when he was clinically well and apparently recovering from his tuberculous infection. He had not received streptomycin for 5 weeks when this occurred.

There was no evidence of urinary tract obstruction. Discounting the two vitamin preparations, only ethambutol and/or isoniazid would seem to have been responsible for the renal dysfunction and histological picture of ADIN. Since this relationship had not been hitherto appreciated, the drug regimen was not altered for a significant period of time. This may have resulted in the incomplete recovery of renal function.

Second case. A 56-year-old man was admitted to the Nashville Veterans Administration Hospital because of night sweats, weight loss, dyspnea on exertion, productive cough, and a chest X ray compatible with cavitary tuberculosis. Initial sputum examinations revealed numerous acid-fast bacilli, and sputum cultures were subsequently positive for *M. tuberculosis*. Cultures of urine and bone marrow were negative. Routine analysis of the urine was unremarkable, the serum creatinine was 1.0 mg/100 ml, and the creatinine clearance was 79 ml/min.

Treatment was initiated with streptomycin, isoniazid, and ethambutol on 28 May 1974. The trade names of the drugs used were the same as those in Case 1. Streptomycin was discontinued after 2 weeks, when a skin rash developed. The rash was treated with hydroxyzine hydrochloride (Atarax, Roerig), 25 mg four times daily for 8 days. Sputum cultures remained positive until month 4 of therapy. The drug dosage and duration are listed in Table 1.

The patient was first noted to have developed renal insufficiency (serum creatinine of 6.5 mg/100 ml and creatinine clearance of 16 ml/min) during week 9 of hospitalization. Renal function had not been tested for the 4 preceding weeks. He had not received hydroxyzine hydrochloride for 5 weeks. His drug therapy at this time included ethambutol, isoniazid, pyridoxine hydrochloride (50 mg daily), ferrous sulfate (300 mg thrice daily), and one multiple vitamin capsule daily. No other drugs were being given. Urine analysis showed eight to ten leukocytes and three to four coarse granular casts per high-power field. An IVP showed no significant abnormalities. A mild hypercalcemia (10.9 to 11.3 mg/100 ml) was also noted at this time. A 24-h urine protein excretion was 2.2 g. Peripheral blood eosinophilia and the course of his renal insufficiency are shown in Fig. 5. Since the eosinophil count was computed by multiplying the total leukocyte count by the percentage of eosinophils, the drop in eosinophilia on about day 60 was thought to be insignificant. Permission for renal biopsy was not obtained. Rifampin was substituted for ethambutol during week 11. The hypercalcemia and urinary sedi-

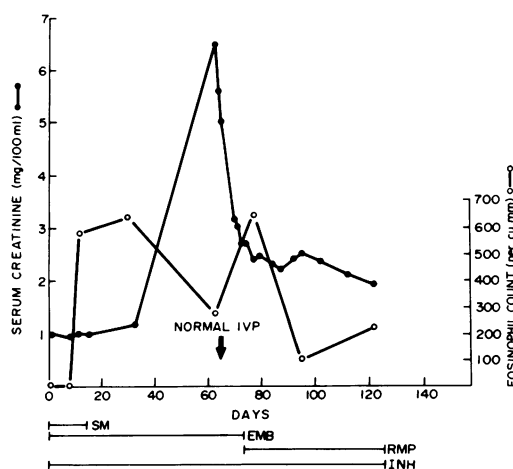


FIG. 5. Clinical course of the second patient in relation to drugs received. Abbreviations are the same as those in the legend to Fig. 1.

ment abnormalities gradually disappeared. The patient was discharged to outpatient follow-up of his pulmonary tuberculosis after 18 weeks of hospitalization. The serum creatinine was 1.9 mg/100 ml, and the creatinine clearance was 38 ml/min at discharge. After 17 months his serum creatinine was 1.7 mg/100 ml.

Comment. This patient was almost identical to the one described in the first case report. Unfortunately, he refused to have a renal biopsy. A skin rash antedated the development of acute renal insufficiency as has been seen with methicillin-induced ADIN (1), which further strengthens our contention. Other than vitamins and iron, he was receiving only isoniazid and ethambutol when renal dysfunction appeared, and there was no evidence of urinary tract obstruction at any time. Withdrawal of the drugs probably causing ADIN was delayed, another agent known to cause ADIN (rifampin) was added, and total recovery of renal function did not occur.

Third case. A 56-year-old man was admitted to the Nashville Veterans Administration Hospital because of fever, weight loss, a chest X ray suggestive of miliary tuberculosis, and a positive PPD skin test. Liver biopsy and bone marrow aspirate revealed granulomas and acid-fast bacilli. A sputum smear was also positive for acid-fast bacilli. On day 2 of hospitalization (26 March 1975), treatment was initiated with isoniazid (Kasar Laboratories) and rifampin (Rifadin; Dow) (Table 1 and Fig. 6). Acetaminophen (Tylenol, McNeil) was used as an antipyretic from days 3 through 6 in a dose of 650 mg every 4 h. Sputum cultures remained positive until week 11 of hospitalization. An initial IVP

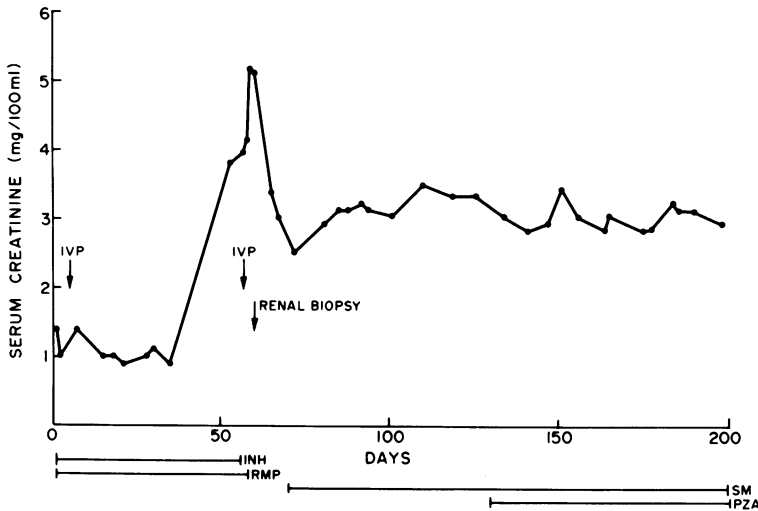


FIG. 6. Clinical course of the third patient in relation to drugs received. Abbreviations are the same as those in the legend to Fig. 1.

was normal, except for a minor irregularity of the right upper pole calyx. One urine culture on day 2 was positive for *M. tuberculosis*, but three subsequent urine cultures between days 3 and 50 were negative. On day 8 he was placed on 10 mg of prednisone every 8 h because of constitutional symptoms and high fever, but this had to be discontinued 10 days later because of signs of acute pancreatitis. On day 53 of hospitalization, the creatinine clearance was noted to have decreased from an admission value of 85 to 23 ml/min. Serial serum creatinine determinations are shown in Fig. 6. There was no increased peripheral blood eosinophilia at any time during his course. Glycosuria and hyperchloremic acidosis were transiently present during week 8. Another IVP was unremarkable except for delayed excretion of contrast material. A renal biopsy on day 60 demonstrated a diffuse, heavy infiltrate of inflammatory cells around tubules in both the cortex and medulla (Fig. 7 and 8). Lymphocytes predominated, but many eosinophils and plasma cells were also seen. There was marked interstitial edema with little fibrosis. Glomeruli and blood vessels appeared normal. No granular deposits or linear staining were demonstrated by immunofluorescent studies with antisera to immunoglobulin A (IgA), IgG, IgM, C₃, and C₄. No deposits were seen on electron microscopy. All antituberculous therapy was stopped. Other drugs administered prior to this included pyridoxine, aluminum-magnesium hydroxide (Riopan, Maalox, Amphojel), a multiple vitamin capsule, folic acid, and vitamin B₁₂. No other drugs were given. By day 70 his creatinine

clearance had improved to 35 ml/min. Streptomycin was begun because of continued fever. Pyrazinamide was added to the regimen on day 129. At about this time an asymptomatic elevation of the serum calcium (11.4 to 13.2 mg/100 ml) was noted but was never well explained. On a low calcium diet and off multiple vitamins (400 U of vitamin D per tablet), this had stabilized at 12 mg/100 ml at the time of discharge on day 205. He was afebrile and was continued on streptomycin, 1 g intramuscularly twice weekly, and pyrazinamide, 1 g twice daily. Recovery of renal function was incomplete (Fig. 6), with creatinine clearances of 30 ml/min at discharge and 37 ml/min 5 months later.

Comment. The chemotherapy this patient received for tuberculosis consisted of only isoniazid and rifampin. He was on no other medications, except vitamins and antacids, when acute loss of renal function occurred. Although rifampin has been reported to cause ADIN (4, 8, 12), this case is included to emphasize the fact that this type of nephrotoxicity can accompany more than one drug regimen for tuberculosis.

DISCUSSION

Renal insufficiency complicating tuberculous infection may be due to (i) advanced parenchymal disease, in which case the intravenous pyelogram is almost always abnormal (15); (ii) obstructive uropathy as a result of urethral cicatrization (implicating drug-induced healing of superficial mucosal lesions); (iii) rarely, streptomycin-induced acute tubular necrosis; and (iv) as mentioned, ADIN complicating drug ther-



FIG. 7. Renal interstitium is edematous and heavily infiltrated with lymphoid cells. The glomerulus shows no abnormalities. Periodic acid-Schiff stain. $\times 160$.

apy. The evidence is substantial against the first three situations in all of the three cases reported herein. The combination of clinical and histological data provides strong support for the presumptive diagnosis of ADIN in all.

As mentioned above, rifampin has been re-

ported to cause ADIN (4, 8, 12), and Rich (13) has attributed one case to streptomycin and isoniazid therapy. In the first two patients reported, it seems unlikely that rifampin could have initiated the process. In these two cases it is possible that streptomycin may have been

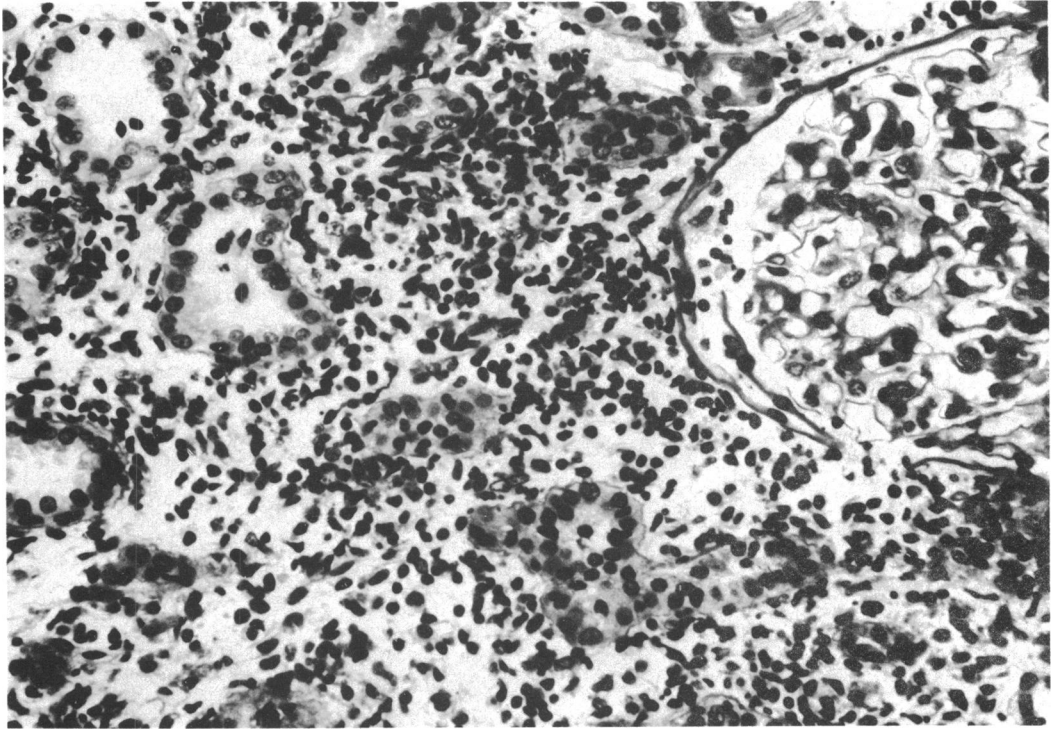


FIG. 8. A normal glomerulus and marked inflammatory cell infiltration of the interstitium are pictured. Periodic acid-Schiff stain. $\times 330$.

the responsible agent, although neither patient had received streptomycin for several weeks at the onset of renal insufficiency. However, it is worth emphasis that streptomycin given as a single agent has never been reported to cause ADIN, and, further, neither have any of the related aminoglycoside antibiotics, which, when they are responsible for renal insufficiency, produce the clinical and histological picture of acute tubular necrosis (9, 11).

By elimination it seems reasonable to suggest that isoniazid and/or ethambutol may have produced the observed abnormalities in the first two patients. It is recognized that the evidence presented is only suggestive and by no means conclusive, especially since recovery in these two cases appeared to commence while the agents were still being administered. However, the concept that drug-induced ADIN progresses as long as the offending agent is being administered is itself largely based on circumstantial evidence and is by no means rigorously established, since in almost all instances drugs are discontinued when the diagnosis is made. However, at least one patient with methicillin-induced ADIN demonstrated improvement in renal function while still receiving the drug (1).

ADIN is a more frequent form of renal injury

than is commonly recognized by most physicians, is being described as a complication of an increasing number of drugs, and is poorly understood in terms of pathogenesis and natural history. This, together with the frequency with which isoniazid and ethambutol are administered, would seem to justify raising the possibility that these drugs may also cause this serious and potentially irreversible type of renal failure.

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